

WEB

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

FISH & RICHARDSON P.C.
Attn. BEATTIE, Ingrid A.
225 Franklin Street
Boston, Massachusetts 02110-2804
UNITED STATES OF AMERICA

RECEIVED

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

DEC 14 1999

(PCT Rule 44.1)

FISH & RICHARDSON, P.C.
BOSTON OFFICE

Date of mailing
(day/month/year)

07/12/1999

DEC 14 1999

Applicant's or agent's file reference

04907021101

FOR FURTHER ACTION

INGRID A. BEATTIE
See paragraphs 1 and 4 below

International application No.

PCT/US 99/15625

International filing date
(day/month/year)

08/07/1999

Applicant

RHODE ISLAND HOSPITAL et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

Reception System
ESP TO RPT 2/7/00
ART (001) 3/7/00
Initials: LXA
Record:

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Véronique Baillou

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 04930/024W01	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 15625	International filing date (day/month/year) 08/07/1999	(Earliest) Priority Date (day/month/year) 10/07/1998
Applicant RHODE ISLAND HOSPITAL et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

1



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

/US 99/15625

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N5/06 C12N5/16 A61M1/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. ALISON ET AL.: "Wound healing in the liver with particular reference to stem cells" PHIL. TRANS. R. SOC. LOND. B, vol. 353, 1998, pages 877-894, XP002123293	18-34, 42
Y	the whole document	1-48
X	✓ M. AGELLI ET AL.: "Putative liver progenitor cells: conditions for long-term survival in culture" HISTOCHEMICAL JOURNAL, vol. 29, 1997, pages 205-217, XP002123294	18-34, 42
Y	the whole document	1-48

	-/--	

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 November 1999

Date of mailing of the international search report

07/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Marie, A

INTERNATIONAL SEARCH REPORT

International Application No

/US 99/15625

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	✓ S. BRILL ET AL.: "Hepatic progenitor populations in embryonic, neonatal and adult liver" P.S.E.B.M., vol. 204, 1993, pages 261-269, XP002040996	18-34,42
Y	the whole document	1-48
X	J.M. LEMIRE ET AL.: "Oval cell proliferation and the origin of small hepatocytes in liver injury induced by D-galactosamine" AMERICAN JOURNAL OF PATHOLOGY, vol. 139, no. 3, 1991, pages 535-552, XP002123295	18-34,42
Y	the whole document	1-48
Y	Y. TIAN ET AL.: "The oval shaped cell as a candidate for a liver stem cell in embryonic, neonatal and precancerous liver: identification based on morphology and pyruvate kinase isoenzyme expression" HISTOCHEM. CELL. BIOL., vol. 107, 1997, pages 243-250, XP002123296	18-34,42
Y	the whole document	1-48
X	S. SELL: "Is there a liver stem cell?" CANCER RESEARCH, vol. 50, 1990, pages 3811-3815, XP002123297	18-34,42
Y	the whole document	1-48
X	M. ALISON: "Liver stem cells: a two compartment system" CURRENT OPINION IN CELL BIOLOGY, vol. 10, 1998, pages 710-715, XP002123298	1-34,42
Y	the whole document	1-48

AUG 02 2000

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BEATTIE, Ingrid A.
FISH & RICHARDSON P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
ETATS-UNIS D'AMERIQUE

RECEIVED

AUG 01 2000

FISH & RICHARDSON, P.C.
BOSTON OFFICE

NOTIFICATION OF TRANSMISSION
OF THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

MINTZ LEVIN, BOSTON
PATENT DOCKET DEPT.

Done By

- ☐ Data Entry
☐ Docket Entry
☐ Docket Cross Off
☐ Previously Entered
☐ No Docketing Req
☐ ELITE
☐ Annuities

Date of mailing
(day/month/year) 20.07.2000

Applicant's or agent's file reference

04990/024WO

21486-024WO

IMPORTANT NOTIFICATION

International application No.
PCT/US99/15625

International filing date (day/month/year)
08/07/1999

Priority date (day/month/year)
10/07/1998

Applicant

RHODE ISLAND HOSPITAL et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

transfer

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Luoma, M

Tel. +49 89 2399-8929



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 5/06, 5/16, A61M 1/14		A1	(11) International Publication Number: WO 00/03001
			(43) International Publication Date: 20 January 2000 (20.01.00)
(21) International Application Number: PCT/US99/15625		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 8 July 1999 (08.07.99)			
(30) Priority Data: 09/113,774 10 July 1998 (10.07.98) US			
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/113,774 (CON) Filed on 10 July 1998 (10.07.98)			
(71) Applicant (for all designated States except US): RHODE ISLAND HOSPITAL [US/US]; 593 Eddy Street, Providence, RI 02903 (US).			
(72) Inventor; and (75) Inventor/Applicant (for US only): FARIS, Ronald, A. [US/US]; 214 Sumter Street, Providence, RI 02907 (US).			
(74) Agent: BEATTIE, Ingrid, A.; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).			

Published

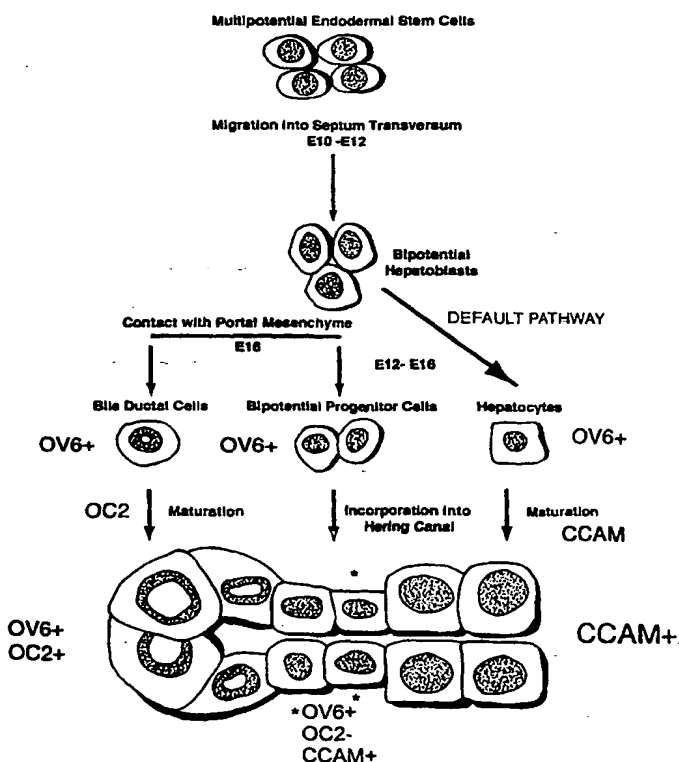
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: LIVER STEM CELL

(57) Abstract

The invention provides a primary liver stem cell and a cell doublet consisting of a hepatocyte and the stem cell, both of which are derived from normal liver tissue. Methods of isolating the cells, genetically altering the cells, and using the cells for transplantation are also within the invention.

ANTIGENIC PATHWAY OF LIVER DEVELOPMENT



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

REC'D 25 JUL 2000

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 04930/024WO1	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/15625	International filing date (day/month/year) 08/07/1999	Priority date (day/month/year) 10/07/1998
International Patent Classification (IPC) or national classification and IPC C12N5/06		
Applicant RHODE ISLAND HOSPITAL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 09/02/2000	Date of completion of this report 20.07.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Marie, A Telephone No. +49 89 2399 8413 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/15625

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-17 as originally filed

Claims, No.:

1-48 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/15625

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims
	No: Claims 1-48
Inventive step (IS)	Yes: Claims
	No: Claims 1-48
Industrial applicability (IA)	Yes: Claims 1-48
	No: Claims

2. Citations and explanations

see separate sheet

1. Various prior art documents are concerned with liver stem cells.

For instance, **Phil. Trans. R. Soc. Lond. B, 1998, 353, 877-894 (D1)** describes cells located in the biliary epithelium, which are the progenitor of the oval cells (chapter 5, page 878- page 880).

Histochemical Journal, 1997, 29, 205-217 (D2) is concerned with the culture of said liver progenitor cells, which appear to be derived from the canals of Hering or from the periductular cells.

P.S.E.B.M., 1993, 204, 261-269 (D3) isolates and cultures cells called OCAP, which are considered as progenitors of the oval cells (page 264).

American Journal of Pathology, 1991, 139/3, 535-552 (D4) concludes on page 550 (left column, last paragraph) that "...duct cells are the likely progenitor of oval cells...".

Histochem. Cell. Biol., 1997, 107, 243-250 (D5) considers some oval-shaped cells to be the progenitors of the oval cells (page 244, left column, or page 247, right column; or chapter "Discussion").

Cancer Research, 1990, 50, 3811-3815 (D6) also identifies such stem cells which are under the form of a cluster of 2 daughter cells (page 3811, left column, last full paragraph or page 3812, right column, last full paragraph).

Current Opinion in Cell Biology, 1998, 10, 710-715 (D7) is also concerned with the identification of liver stem cells which are the progenitors of oval cells. Said stem cells are supposed to be placed in the canals of Hering.

D1 and **D7** indicate that said stem cells may be useful vehicles for *ex vivo* gene therapy.

2. It seems that the subject-matter of claims 1-17 is mostly novelty-destroyed (Article 33.2 PCT) by the disclosure of at least **D7**, which shows a doublet between the stem cell and the hepatocyte and suggests the use of said stem cells in gene

therapy.

In this context, it has to be kept in mind that the characterization of a known substance by other parameters than those found in the prior art does not necessarily render said known substance novel. The burden of the proof lies in this case on the applicant, who should demonstrate that the stem cells of the prior art do not exhibit the antigens listed in the present claims.

If it had to be considered that the disclosure of **D7** is too speculative to be novelty-destroying, then **D7** would at least imply a lack of inventive step for said claims 1-17 (Article 33.3 PCT).

Furthermore, the disclosure of the cell doublet in **D7** renders the subject-matter of claims 35-41 non-inventive (Article 33.3 PCT), since the existence of such a cell doublet strongly suggests the use of said doublet to purify the stem cell and/or the hepatocyte.

3. The subject-matter of claims 18-34, 42 is novelty-destroyed (Article 33.2 PCT) by the disclosure of **D1-D7**, which are all concerned with stem cells.
4. The need of liver assist devices for people suffering from liver injury is well established and the usefulness of liver stem cells and/or hepatocytes therefor is obvious for the skilled man. Therefore, claims 43-44 are not based on an inventive concept (Article 33.3 PCT).
5. Claims 45-48, which could under certain patent laws give rise to objections because they refer to methods of treatment of the human body, are also not novel (Article 33.2 PCT) and/or do not involve an inventive step (Article 33.3 PCT) in view of the disclosure of **D1-D7**.